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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
02/18/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/587,816	OLESEN ET AL.	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *27-32 and 35-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/23/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-26 and 32-34, and species election of amyloid beta peptides, in the reply filed on November 30, 2009 is acknowledged.

Upon further review, it is noted that claim 32, which recites the "use of a conjugate as defined in claim 1…for the treatment and/or prophylaxis of an amyloid-related disease", was inadvertently included in Group I in the restriction requirement. This claim relates to a treatment method instead of a product, and should have been included in Group II instead of Group I. Accordingly, this claim has been reassigned to Group II and is withdrawn from consideration.

2. Claims 27-32 and 35-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 30, 2009.

3. Claims **1-26** and **33-34**, to the extent the read upon the elected species of amyloid beta peptides, are under examination in the present office action.

Information Disclosure Statement

4. The information disclosure statement (IDS) filed October 23, 2006 has been considered. The Lemere et al. (2004) reference has not been considered because no copy of this reference has been provided; this reference has been lined through.

Specification

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of C.F.R. §§ 1.821-1.825. The disclosure contains sequences that require reference to particular sequence identifier numbers (SEQ ID NO:), such as on pages 10, 19, 28, and 36. In case these sequences are not in the originally filed sequence listing, Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", and amendment directing the entry of that paper copy into the specification, and where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Claim Objections

6. Claim 19 is objected to because of the following informalities: the claim is missing a hyphen between the numbers 1 and 42 in the phrase "amyloid beta (1 42)" (*sic*). Appropriate correction is required.

7. Claim 25 is objected to because of the following informalities: the claim contains peptide sequences that require sequence identifier numbers (SEQ ID NOs). Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 recites that the amyloid protein fragment of the conjugate is a region comprising the "C-terminal region, beta sheet region, cytotoxic region, GAG-binding site region, or macrophage adherence region". However, none of these regions are clearly defined by the specification as to which peptide fragments of the various amyloid proteins they encompass. While a "C-terminal region" may be understood by one of ordinary skill in the art, even for the well-described amyloid-beta peptide, there is not a strong consensus in the art as to what comprises a "cytotoxic region". For example, various groups have determined that potentially all fragments as well as full-length versions of Aβ can be considered toxic to neurons depending on the assay system involved. Additionally, while a core sequence of peptides (e.g., Aβ 13-16) may be associated with the "beta sheet region" or "GAG-binding site region" of Aβ, there is also a lack of consensus in the art as to the extent of these regions, or whether they are

better defined in terms of their tertiary structural motifs. Moreover, the art to which the instant invention pertains is silent with respect to a "macrophage adherence region" for the Aβ peptide. Therefore, the various recitations of "cytotoxic region", "GAG-binding site region", "beta sheet region", and "macrophage adherence region" render the claim vague and indefinite with respect to the peptide sequences comprised therein. The metes and bounds of the conjugate of claim 5 thus cannot be determined.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-26, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/72880 A2 by Schenk et al. (published 7 December 2000), US 2003/0073655 A1 by Chain (published 17 April 2003) and US 2003/0157117 A1 by Rasmussen et al. (published 21 August 2003), all in view of WO 00/18791 by Holm et al. (published 6 April 2000).

The teachings of Schenk et al., Chain, and Rasmussen et al. are commensurate in scope and are presented to establish the general knowledge available to one of ordinary skill in the art at the time the invention was filed. Each of the references teach immunogenic conjugates of amyloid-beta (Aβ) peptide fragments, such as for incorporation in pharmaceutical compositions or vaccines for induction of an immunogenic (antibody) response against Aβ upon administration to a subject, which is useful for the treatment of a disease associated with amyloid deposits (see, for example, Schenk at p. 5, lines 12-16, or Rasmussen at [0056]). These teachings address limitations of claim 2, which recite that upon administration of the claimed conjugate to a mammal, the conjugate is capable of eliciting a production of antibodies having specificity towards the conjugate itself, and inducing an immune response in the mammal such as for therapeutic purposes.

Schenk teaches that the immunogenic agents of the invention comprise fragments of Aβ peptide linked to a suitable carrier protein to help elicit an immune response. Suitable carriers are taught to include serum albumins, keyhole limpet hemocyanin, or tetanus toxoid (p. 28, lines 17-19), including the T-cell epitopes of the tetanus toxoid fragments of $TT_{947-967}$ (FNNFTVSFWLRVPKVSASHLE) and $TT_{830-844}$ (QYIKANSKFIGITEL) (p. 28, lines 30-31), thus addressing limitations of what X may represent as in claims 24-26. Regarding claims 33-34, pharmaceutical compositions are taught to comprise these immunogenic Aβ conjugates along with an adjuvant (p. 38, lines 32-33), wherein suitable adjuvants include complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) (p. 40, lines 9-10), QS21 (p. 40, line 7), aluminum hydroxide (p. 39, lines 19-20), or MF59 (p. 39, line 30). Schenk discloses multiple antigen peptide (MAP4) configurations comprising segments of Aβ linked to carrier peptides on a branched structure (see pp. 30-31) for presentation of the immunogenic conjugates. This multiplicity of antigens, Schenk notes, greatly enhances the responsiveness of B cells to the antigen (p. 30, line 29).

With respect to the Aβ peptides, Schenk teaches that Aβ has several naturally-occurring forms, including Aβ39, Aβ40, Aβ41, Aβ42, and Aβ43 (p. 14, lines 9-10), which addresses the amyloid proteins of claims 6 and 7. In addition, Schenk teaches that immunogenic fragments of Aβ have a sequence of at least 2, 3, 5, 6 or 10 contiguous amino acids from a natural peptide, or has no more than 10, 9, 8, 7, 5 or 3 contiguous residues from Aβ (p. 14, lines 30-32). Such teachings are on point to recitations of peptide fragment length in present claims 10-17. One disclosed fragment is the C-

terminal fragment Aβ35-42 (p. 15, line 7), which is a fragment of 8 amino acids from the C-terminus of amyloid beta, thus meeting limitations of present claims 8 (a fragment of Aβ1-42), 9 (a C-terminus of amyloid beta), 12 (8 amino acids from the C-terminus), and 18 (the fragment is Aβ35-42).

Consistent with the teachings of Schenk, Chain teaches the use of certain antigenic sequences of the amyloid β peptide corresponding to short regions at the C-terminus of Aβ for use in immunization of an animal and the generation of C-terminal-specific antibodies (see [0076] and [0079]). For example, Chain discloses that the peptides can be designed for eliciting antibodies targeted to specific Aβ42 species, and include such targeted sequences as Aβ36-42 and Aβ37-42 (see [0076]), which address limitations of instant claims 13-14 and 19-20. Chain also teaches coupling immunogenic fragments of Aβ to a carrier protein, such as KLH or BSA to enhance the immunogenicity of the conjugate (see [0080]).

Similarly, Rasmussen discloses various antigenic Aβ peptides and immunogenic conjugates thereof, and the preparation of such vaccines for the prevention and treatment of the symptoms of diseases associated with amyloid deposits (see [0056-0057]). Rasmussen teaches that the conjugate comprises at least one copy of a subsequence of amyloid precursor protein (APP) or amyloid beta that has at least one B-cell epitope, and at least one foreign T-helper epitope (T_H epitope) (see [0057-0058]). Suitable B-cell epitope carrying regions of the APP or Aβ peptide are taught to be constituted by short peptide stretches that in no way would be able to bind productively to an MHC Class II molecule, and should therefore comprise at most 9 consecutive

amino acid residues. Shorter peptides are preferred, such as those having at most 8, 7, 6, 5, 4, or 3 consecutive amino acids from the amyloidogenic polypeptide's amino acid sequence (see [0147]). Rasmussen thus teaches peptides comprising at least one subsequence of SEQ ID NO: 2 (this is the sequence for APP), wherein the peptide consists of 9, 8, 7, 6, 5, 4 or 3 consecutive amino acids, and wherein the consecutive amino acids begin at an amino acid residue selected from the group consisting of residue 707, 708, 709, 710, 711 and 712 of SEQ ID NO: 2 (see [0148-0149]). It is noted that residues 672-714 of APP (Rasmussen's SEQ ID NO: 2) are residues 1-42 of the Aβ peptide. Therefore, residues 707, 708, 709, 710, 711 and 712 of SEQ ID NO: 2 correspond to residues 35, 36, 37, 38, 39, and 40 of Aβ42, respectively. Accordingly, these teachings provide for Aβ peptide fragments of Aβ 35-42, 36-42, 37-42, 38-42, 39-42 and 40-42 as in claims 18-23, and C-terminal Aβ fragments of specific recited lengths, as in claims 11-17. Such would also address limitations of claims 4 and 5, reciting for example that fragment comprise a C-terminal region of an amyloid protein. Rasmussen also discusses various immunogen carriers comprising a T_H epitope (see [0123-0134] and [0242-0244]) and suitable means for coupling the carrier to the Aβ peptide, such as a polyhydroxypolymer carrier (for example, at [0245-0266]).

Taken together, the teachings of Schenk, Chain, and Rasmussen provide for conjugates comprising C-terminal fragments of Aβ preferentially linked to immunogenic carrier proteins, such as a T_H-cell epitope, for induction of an immune response (i.e., an antibody response) against Aβ in a subject. Although the references teach various constructs for such immunogenic conjugates, such as the MAP configuration, the

difference between the prior art teachings of the above references and the present invention is that the references do not teach a conjugate having the structure recited in claim 1, or that the peptides are C-terminally presented (as in claim 3).

Holm et al. teach methods for preparing a ligand presenting assembly (LPA) and immunological compositions and vaccines thereof for generating antibodies (see abstract). Holm reviews the various means for coupling peptides to carriers, including the use of dendritic polymers such as the multiple antigen peptide (MAP) configuration. In reviewing the different methods for production of MAPs, Holm highlights the problems of these constructs and their different means of production, wherein the resultant constructs may not be chemically homogenous and/or wherein the C to N orientation of the antigen on the MAP configuration may hinder recognition of dominant (or subdominant) epitopes on the C-terminal of peptide (see Background of the Invention, pp. 1-7). Thus, Holm's disclosed LPAs allow for peptides with N to C orientation, such that B cell epitopes on the C-terminus may be exposed (see p. 18).

Holm teaches a construct consistent with the presently recited structure of claim 1. For example, the general formula of: $X[(A)_nCOOH][(B)_mCOOH]$, wherein n and m are 0 or an integer of from 1 to 20, X is $H_2N(CR_2)p$ or $RHN(CR_2)p$, wherein p is an integer from 0-20, R is H, etc., and A and B together form a substituted or unsubstituted cyclic moiety, etc. is taught at pp. 15-16. By reaction with a carboxylic acid, a construct of the following type is formed: $X(CO\text{-sequence})_2$-solid phase, wherein "sequence" is a peptide sequence comprising naturally occurring and/or non-naturally occurring amino acids (p. 17, lines 21-29). Taken together, for example, such a structure would include

the formula of: $H_2NCH(CO\text{-}NH\text{-}peptide\text{-}OH)_2$, which is consistent with the structure of claim 1 wherein R is –NHCH<, X is a hydrogen, L_A is optionally not present, L_B is optionally not present, P is a peptide, and Y is OH. One such example disclosed by Holm is Figure 5, which is $NH_2CH(CH_2CO\text{-}ProValValAlaGluSerProLysLysPro\text{-}OH)_2$. In this case and in the formula above, the peptide sequences (e.g., PVVAESPKKP) are C-terminally presented, thus addressing instant claim 3. Holm additionally teaches that LPAs allow for continued synthesis or fragment coupling of a sequence different from the first peptide, such as a T cell epitope, to produce a chimeric product comprising both B and T cell epitopes (p. 18, lines 17-19 and p. 28, lines 24-29).

It would have been obvious to one of ordinary skill in the art at the time the invention was filed to modify the immunogenic conjugate comprising Aβ peptide fragments as taught by Schenk, Chain, and Rasmussen, according to the immunogenic construct as taught by Holm to arrive at the claimed invention. Each of Schenk, Chain and Rasmussen teach the use of C-terminal fragments of Aβ which comprise B-cell epitopes, and conjugation of these peptide sequences to an immunogenic construct, preferably with a carrier protein such as a T_H cell epitope. Based on the teachings of Holm et al., the skilled artisan would have been aware of the benefit in using the LPA construct for the presentation of C-terminal peptides, because the N to C orientation of the construct allows for recognition of epitopes on the C-terminus (whereas the MAP configuration typically is a C to N configuration, which hinders recognition of C-terminal epitopes on peptide sequences). Thus, it would have been *prima facie* obvious to produce a conjugate according to the structure of claim 1. Thus is because the skilled

artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to the use of a known technique (Holm's method of preparing LPAs) to improve similar products (i.e., immunogenic Aβ conjugates) in the same way to yield predictable results.

Conclusion

12. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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